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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

MEHTA, ASHWIN D

ART UNIT PAPER NUMBER

1638

DATE MAILED: 07 15 2002

12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/715,294

Applicant(s)

YADAV, NARENDRA S.

Examiner

Ashwin Mehta

Art Unit

1638

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 April 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 36-43, 70 and 80 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 36-43, 70 and 80 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☒ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 235
7, 8, 9
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group IV, claims 36-43, 70, and 80 in Paper No. 11 is acknowledged. Note that non-elected subject matter encompassed by claims 70 and 80 should be removed.

Priority

2. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The first sentence on page 1 of the specification indicates that the instant application is a continuation-in-part of U.S. application 09/442,021. However, no mention is made of the other continuing applications, their filing dates, and status (pending, patented, or abandoned).

Information Disclosure Statement

3. Several citations in the IDSs submitted 25 January 2001 and 16 April 2001 have been lined through, only because they already appear, and have been initialed by the Examiner in the other IDSs.

Drawings

4. Information on how to effect drawing changes: Note that this information replaces the information that appears on the back of the accompanying form PTO-948.

Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in **ABANDONMENT** of the application.

Claim Objections

5. Claim 38 is objected to for the following minor informality: the term --of-- appears to be missing in line 2 of part 3) of the claim, before "P1".

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

Art Unit: 1638

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 36-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 36-39: the preambles of claims 36-39 indicate that the methods are for conditionally activating a transgene in a second generation plant. However, part 4) of each of the claims indicates that R2 can be expressed in the first generation plant. As R2 excises the STP fragment flanked by RS2 sites in the third recombinase element, transcription of the transgene will be activated in the first generation plants. This is not consistent with the preamble of the claims.

Part 1) of each of claims 37 and 39 render the claims indefinite. Part 1) of the claims indicates that a construct is provided that comprises three recombinase elements. However, it is not clear whether or not all three recombinase elements are supposed to be in the same construct. Part 1) indicates that they are. However, in claim 37 for example, part 2) indicates that a transgenic plant comprises only the third element, and part 3) indicates that the plant is to be transformed with the second element, or the third element, which suggests that the three recombinase elements cannot be comprised within the same construct. In claim 39, parts 2) and 3) indicate that separate plants comprises the first and third elements, and the second and third elements, again indicating that the three elements are not located on the same construct. Part 1) of claims 37 and 39 should be amended to clearly indicate whether or not all three recombinase elements must be located in the same construct.

Application/Control Number: 09/715,294

Art Unit: 1638

Further in claim 37: Parts 2)- 4) of the claims render the claims indefinite. Part 4) indicates that the first and second plants of parts 2) and 3) are to be crossed such that expression of R1, which is in the first recombinase element, occurs. However, neither the first or second plant has the first recombinase element. For purposes of examination, the Examiner is assuming that the transgenic plant of part 2) of claim 37 comprises the first, rather than the third, recombinase element, as this is consistent with part 4) of the claim.

Further in claim 39: Parts 1c) and 4) of the claim renders it indefinite. Part 1c) indicates that the third recombinase element is to be chosen from a Markush group consisting of two general structures, indicating that the third recombinase element has only one of these structures. However, part 4) of the claim indicates that the transgenes located on the different general structures are both expressed, which indicates that both of the general structures mentioned in part 1c) make up the third recombinase element. It is not clear whether the third recombinase element is to comprise only one or both of the general structures mentioned in part 1c).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 36-38 and 43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for conditionally activating a transgene in a second generation plant when the promoter of the third recombinase element is not active in the common germline, does not reasonably provide enablement for the claimed methods when the

Art Unit: 1638

promoter of the third recombinase element is active in the common germline. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are broadly drawn towards a method for conditionally activating a transgene in a second generation plant comprising 1) providing a construct comprising a first recombinase element having a promoter, P1 operably linked to a recombinase, R1, a second recombinase element comprising the general structure P2-RS1-STP-RS1-R2, and a third recombinase element having the general structure P3-RS2-STP-RS2-TG, wherein a transgenic plant is provided that comprises the three recombinase elements, and activating P1 such that R1 is expressed in the common germline of a first generation plant and excises the STP fragment from the second recombinase element, activating P2 to express R2 in the common germline of the first or second generation plant, wherein R2 excises the STP fragment from the third recombinase element, allowing expression the transgene in the second and subsequence generations of plants; or wherein the method comprises providing a transgenic plant comprising the first recombinase element and crossing it with a plant comprising either the second element to generate a first plant or a third recombinase element to generate a second plant, and crossing the first and second plants.

The specification teaches combinations of two site-directed recombination systems to cause developmentally staggered site-specific recombinations to control expression of a transgene in a plant. One of the recombinases would remove a stop or blocking fragment that lies between a second recombinase-encoding gene and its promoter. The two recombinases can be expressed at different points in plant development. The second recombinase can then remove

Art Unit: 1638

a stop fragment located in between a transgene and its promoter. The salient feature is that expression of the second recombinase or the transgene does not have to occur immediately upon removal of the stop fragment, but is controlled by the choice of the promoters (page 35, line 4 to page 36, line 30).

However, the specification does not enable the claimed methods when the promoter in the third recombinase element, which comprises the transgene, is active in the germline. The claims indicate that the first and second promoters are active in the common germline. No restriction is indicated for the nature of the P3 promoter. If the third promoter is also active in the common germline, then removal of the STP fragment from the third recombinase element will activate transcription of the transgene. While this will allow expression of the transgene in the second generation plants, expression would have been activated in the first generation. The claims, however, specifically call for activating the transgene in the second generation. Undue experimentation would be required by one skilled in the art to use the claimed method to prevent activating expression of the transgene in the first generation plants if the promoter of the third recombinase element is active in the common germline. See Genentech, Inc. V. Novo Nordisk, A/S, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997), which teaches that "the specification, not the knowledge of one skilled in the art" must supply the enabling aspects of the invention. It is suggested that the claims be amended to indicate that P3 is not active in common germline. Given the breadth of the claims encompassing the use of any promoter as the P3 promoter, unpredictability of the art and lack of guidance of the specification as discussed above, undue experimentation would be required by one skilled in the art to make and use the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. Claims 36-43, 70, and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Odell et al. "A" (Mol. Gen. Genet., 1990, Vol., 223, pages 369-378) in combination with Lloyd et al. (Mol. Gen. Genet., 1994, Vol. 242, pages 653-657), Applicant's admitted state of the prior art, and Odell et al. "B" (Use of Site-Specific Recombination Systems in Plants, in Homologous Recombination and Gene Silencing in Plants, 1994, pages 219-270, Ed. Paszkowski, J., Publisher: Kluwer, Dordrecht, Germany).

The claims are broadly drawn towards a method for conditionally activating a transgene in a second generation plant comprising 1) providing a construct comprising a first recombinase element having a promoter, P1 operably linked to a recombinase, R1, a second recombinase element comprising the general structure P2-RS1-STP-RS1-R2, and a third recombinase element having the general structure P3-RS2-STP-RS2-TG, wherein a transgenic plant is provided that comprises the three recombinase elements, and activating P1 such that R1 is expressed in the common germline of a first generation plant and excises the STP fragment from the second recombinase element, activating P2 to express R2 in the common germline of the first or second generation plant, wherein R2 excises the STP fragment from the third recombinase element,

Art Unit: 1638

allowing expression the transgene in the second and subsequent generations of plants; or wherein P1 is a common germline promoter, P2 is a floral common germline promoter, and P3 is seed-specific; or wherein the method comprises providing a transgenic plant comprising the first recombinase element and crossing it with a plant comprising either the second element to generate a first plant or a third recombinase element to generate a second plant, and crossing the first and second plants; or wherein P1 is inducible in response to an inducing agent; or wherein the third recombinase element is selected from the group consisting of the general structures P3-RS2-STP-RS2-TG1 and P4-RS2-STP-RS2-TG2; or wherein P3 is expressed earlier in the plant life cycle than P4 in the second generation.

Odell et al. A teach use of the Cre/lox recombination system in transgenic tobacco. Plants were stably transformed with a construct comprising the Cre recombinase coding region operably linked to the CaMV 35S promoter and the 3' region of the nopaline synthase gene or a CaMV 3' sequence. Plants were also stably transformed with a vector comprising a fragment that includes the Rubisco small subunit gene polyadenylation signal flanked by loxP sites oriented in the same direction and placed between the NOS promoter and the neomycin phosphotransferase (NptII) coding region. The transgenic plants comprising the "loxP vector" were re-transformed with the Cre-vector. The subsequent transgenic plants were able to grow on kanamycin, indicating that Cre removed the sequence flanked by the loxP sites, thereby allowing expression of NptII. The transgenic plants comprising either the Cre-vector or the loxP vector were also crossed to unite the Cre recombinase and the loxP sites. Kanamycin resistant progeny were obtained. Odell et al. also teach that turning on expression of a marker gene by controlling

Art Unit: 1638

cre expression in a developmental or tissue-specific manner would provide the ability to follow cell lineages in the plant (pages 372-377).

Odell et al. A do not teach a second site-specific recombination system active in plants, inducible promoters or tissue specific promoters.

Lloyd et al. teach use of the FLP/FRT site-specific recombination system in stably transformed tobacco plants. Tobacco plants were transformed with a construct comprising 2.8 kb of a spacer sequence flanked by FRT sites, placed between the CaMV 35S promoter and hph gene. The presence of the 2.8 kb spacer prevented expression of the hph gene in the plant. Plants were also transformed with a construct comprising the FLP coding sequence operably linked to the CaMV 35S promoter. Plants were either re-transformed with the FLP or FRT site-containing plasmid, or crossed, so that plants comprising both FLP coding sequence and FRT sites were generated. Progeny plants were hygromycin resistant, indicating that FLP-mediated recombination removed the 2.8 kb spacer flanked by the FRT sites and allowed expressing of the hph gene (page 656).

Applicant's admitted state of the prior art teaches tissue specific promoters, including seed-specific promoters such as the vicilin promoter, common germline promoters such as the TA29 promoter, floral common germline promoters such as Erecta, inducible promoter systems such as the glucocorticoid system, various types transgenes, including those such as IPT that affect a plant trait, genes that can be used to confer male sterility, including barnase (page 19, lines 30-34; page 23, line 12 to page 25 line 31; page 27, line 27 to page 29, line 14; page 46, lines 15-21).

Odell et al. B discuss uses of site-specific recombination systems in plants, including the Cre/lox, FLP/FRT, R/RS, and Gin/Gix. Odell et al. B assert that the versatility and high recombination frequency of these systems allow their use as tools for a wide range of studies and applications, that the systems can be used to introduce a gene into a plant in an inactive state, and then activate it by recombination when expression is desired, by removing a blocking fragment which can be inserted between the promoter and coding region; that an inactive transgene can be maintained for any number of generations until a recombinase is introduced, and that such characteristics may be advantageous when transgene expression may be detrimental to cell function; when a tissue-specific promoter is used with an inactive transgene, the gene may be activated in only a portion of the cells of the tissue by reducing efficiency of recombination. The recombinase can be introduced by transforming a recombinase gene into a plant that already has the target sites integrated in the genome, or by genetic crosses between recombinase gene-containing and target site-containing plants; the recombinase gene can also be regulated by an inducible or tissue-specific promoter, if constitutive expression is not desired (pages 224-226, 234-246, 255-262).

It would have been obvious and within the scope of one of ordinary skill in the art at the time the invention was made to use site-specific recombination systems, such as the Cre/lox system taught by Odell et al. A and the FLP/FRT system taught by Lloyd et al., to control the timing of expression of a transgene in a plant. It would have been obvious to introduce into a plant 1) a first construct comprising a promoter active in the common germline, such as those taught by Applicant's admitted state of the prior art, operably linked to a first recombinase coding sequence, for example the Cre recombinase; 2) a second construct comprising one of the

Art Unit: 1638

aforementioned promoters or a flora germline promoter, such as the Erecta promoter taught in Applicant's admitted state of the prior art, and a second recombinase coding sequence, for example the FLP recombinase, wherein the promoter is separated from the FLP coding sequence by a blocking or STP fragment, such as the Rubisco small subunit gene polyadenylation signal used by Odell et al. A, wherein the blocking fragment is flanked by loxP sites; and a third construct comprising a promoter that is not active in common germline, such as the seed specific vicilin promoter taught by Applicant's admitted state of the prior art, and a transgene of interest, wherein the promoter and transgene are separated by a blocking fragment that is flanked by FRT sites. While expression of the first recombinase would remove the blocking fragment of the second construct, and allow expression of the second recombinase which will remove the DNA molecule that is the blocking fragment flanked by the FRT sites from the third construct, thereby operably linking the transgene with its promoter, the transgene would not be active until the next generation of plants as its promoter is not active in the common germline. Alternatively, it also would have been obvious to introduce the constructs into two different plants, for example inserting the first construct and second or first and third constructs into one plant and the other construct into a second plant, and bring them together within the same genome by genetic crosses, as taught by Odell et al. A and Lloyd et al. As numerous different types of promoters are known and used in the prior art, one could also have used an inducible promoter, such as those of the glucocorticoid or any other inducible promoter system taught by Applicant's admitted state of the prior art, to control the timing of expression of the promoter of the first construct, and therefore the timing of expression of the second recombinase and transgene. The choice of promoter amounts to an optimization of process parameters, and depends on one's

Art Unit: 1638

desired result. It would also have been obvious that other constructs with the same design as the third construct may also be included in the method, so as to express further transgenes. Any desired transgene may have been expressed, including those that affect a trait of the plant, such as the IPT gene or barnase, taught by Applicant's admitted state of the prior art. It would also have been obvious that the promoters used to express the transgenes could be active at different points of the plant life cycle, for example with the use of one of the tissue-specific and/or inducible promoters taught by Applicant's admitted state of the prior art, depending on one's desired end. It would also have been obvious that any site-specific recombination system operable in plants, such as those discussed by Odell et al. B, could have been used. One would have been motivated to use site-specific recombination systems to control transgene expression, given the assertion of Odell et al. B that the versatility of these systems and their high recombination efficiency allow their use for a wide range of applications, that they allow transgenes to be maintained in an inactive state for any number of generations, that such characteristics may be advantageous when transgene expression may be detrimental to cell function.

9. No claim is allowed.


Contact Information

Any inquiry concerning this or earlier communications from the examiner should be directed to Ashwin Mehta, whose telephone number is 703-306-4540. The examiner can normally be reached on Mondays-Thursdays and alternate Fridays from 8:00 A.M to 5:30 P.M.

Art Unit: 1638

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at 703-306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 and 703-872-9306 for regular communications and 703-872-9307 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

July 12, 2002


ASHWIN D. MEHTA, PH.D
PATENT EXAMINER

Attachment for PTO-948 (Rev. 03/01, or earlier)

6/18/01

The below text replaces the pre-printed text under the heading, "Information on How to Effect Drawing Changes," on the back of the PTO-948 (Rev. 03/01, or earlier) form.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the Notice of Allowability. Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136(a) or (b) for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit the drawing corrections within the time period set in the attached Office communication. See 37 CFR 1.85(a).

Failure to take corrective action within the set period will result in **ABANDONMENT** of the application.